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The Use of Traditional Chinese Medicine and its Possible
Relationship with Adherence to Highly-active
Anti-Retroviral Therapy in Patients with HIV/AIDS in Hong Kong

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfilment of the Requirement for the
Degree of Doctor of Medicine

by

Kurtland Ma

With: Elsie Chu, Kaveh Khoshnood, Michele Barry, KH Wong, and SS Lee

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Abstract

The aim of this project was to examine the usage of traditional Chinese medicine (TCM) and its possible relation to adherence to HAART by HIV-infected Chinese male patients by answering the following questions:

1. How prevalent is TCM use among HIV-infected Chinese patients?
2. What types of TCM are used by this population?
3. What are the predictors of TCM use in this population?
4. Is there a relationship between TCM use and adherence to HAART?

A total of 81 self-administered questionnaires were completed by ethnic Chinese patients who had been on HAART for at least one year at Integrated Treatment Centre, a public HIV clinic run by the Hong Kong Department of Health.

Amongst study participants, 62% (n=50) reported having taken any form of TCM at least once. A total of thirty forms of TCM were used by the 50 TCM-using patients, of which, 26% (n=13) were Infrequent Users while 72% (n=36) were Regular Users. The most frequent forms were: prescriptions provided by TCM practitioners (56%, n=28), over-the-counter TCM preparations (52%, n=26), and used herbal teas (28%, n=14). During the month preceding the study, 67% of participants (n=54) had full HAART adherence and 33% patients (n=27) reported having missed one dose or more.

Results did not suggest any definite relationship between TCM use and HAART adherence. However, we did find a wide range of forms of TCM used by this patient population. Further, our findings suggest that TCM use among participants was not used to treat HIV/AIDS or related complications. Further study is needed to understand the biological activity of these TCM remedies and any possible interactions with HAART.

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Introduction

The study's aim was to investigate the relationship between the use of Traditional Chinese medicine (TCM) and adherence to HAART in HIV-positive patients in Hong Kong. Our hypothesis was that HIV-positive patients in our clinic who used TCM would have lower levels of HAART adherence because of the increased burden of medication. The study aimed to prove this hypothesis through a self-administered questionnaire that would also probe how and why these patients used TCM and which forms of TCM were used. These data would not only grant us a deeper understanding of the actual medical practices of these individuals, but also grant insight into how to design medical regimens that are congruous with patients' medical beliefs and their everyday practices.

Although 95% of its 7 million habitants are ethnic Chinese, Hong Kong's medical system is predominantly based on a Western-model of healthcare established during the British sovereignty from 1842 to 1997. (Tang & Wong, 1998) In addition to the territory's 12 private hospitals, the Hospital Authority operates more than 50 public hospitals and 74 primary care clinics. The Department of Health oversees health policy as well as preventative and rehabilitative services. All of these services are built upon the principles and technology of Western medicine. Nevertheless, a medical pluralism exists in that the streets are also lined with the influence Traditional Chinese Medicine (TCM), including: fee-for-service herbal shops, acupuncture, and bone-setters. The culture of the people, too, not only draws patients to seeking medical care and expertise outside of the realm of Western medicine. This juxtaposition of East and West, modern and traditional, evidence-based and custom-based that makes Hong Kong a singular environment to study the culture of medicine.

Amongst the Chinese population of Hong Kong, the great majority are Cantonese-speakers from either the *Hakka* or *Teochew* ethnic origins. While Cantonese is the Chinese dialect spoken most, English is also an official language. In fact, while most patient interactions take place in Chinese, most medical teaching—including lectures and meetings—is done in English. However, medical practitioners must also be capable of caring for the great variety of non-Chinese, non-English-speaking individuals from places such as the Philippines, Indonesia, Indian, Pakistan, and Vietnam (Census and Statistics Department, 2007).

Western evidence-based medicine is the primary medical approach supported and offered by the Hong Kong government. All other practices, including TCM and other folk remedies, are offered – in abundance—by the private sector only (Lo et al, 1994). As a result, only Western medical care is offered to HIV/AIDS patients by the

Department of Health's largely-subsidized HIV/AIDS care centers. However, the government has recently begun efforts to oversee and integrate other forms of medicine, which – currently—remain largely unregulated and unsanctioned.

Usage of Traditional Chinese Medicine (TCM) by the adult Chinese population has been reported between 10% (Wong et al., 1993) and 13.5% (Lau et al, 2001), although research estimates 50-60% of people in Hong Kong has consulted TCM practitioners at least once (Tang and Wong, 1998). Chronic disease was one factor found to be significantly related to use of TCM (Lau et al, 2001).

In the Lau et al. study, 3,355 secondary students completed a self-administered questionnaire regarding episodes of illness in the preceding 3 months. Notably the authors only asked about a limited list of illnesses, and included: “cough, cold and/or influenza, digestive system disorders, fall-related injuries, cuts, burns and other injuries, headaches and/or dizziness, chronic anxiety and/or insomnia, skin disease, chronic acne, liver disease, and asthma”. The questionnaire also inquired whether patients sought Western medical care or TCM, and patient perceptions of the effectiveness, cost, and trustworthiness of Western medicine and practitioners. Also, as the study targeted adolescents, participants were asked whether their parents usually chose their doctors for them.

The results indicated that of the 3,355 students, 78.3% (95% CI, 76.9 to 79.9%) had suffered from one of the listed illnesses in the past 3 months, and 48.6% (95% CI, 47.0 to 50.0%) had visited either a Western or TCM practitioner. Of those that had sought professional care, the vast majority (82.1%) had only visited a Western physician. Whereas 5.6% of adolescents had visited a TCM practitioner only and 12.1% had visited both.

The nature of the illness dictated the type of practitioner consulted by students. Patient with skin diseases (5.4%; 95% CI, 2.5% to 9.9%) and fall-related injuries (4.8%; 95% CI, 2.7% to 7.8%) were more likely to consult both TCM and Western practitioners compared to patients with other diseases (<3%). With these results, the authors suggested these patients that saw both types of practitioners were patients that had likely sought TCM care for skin conditions that subsequently worsened with TCM medications thus requiring follow-up treatment by Western practitioners.

The questionnaire results indicated that the demographic factors queried had little value in determining what type of medical care was sought by these students. The decision regarding seeking Western medical care versus TCM did not have statistically significant associations with age ($P = 0.951$ by κ^2 test), father's educational attainment ($P = 0.419$), father's employment status ($P = 0.400$), type of residence $P = 0.711$, or birthplace ($P = 0.494$). Nor did the decision have a statistically significant association with the students' attitudes regarding the

effectiveness of Western medicine, ($P = 0.230$), the capability of Western doctors ($P = 0.374$), the effectiveness of Western prescribed drugs (P value not given), trust in Western doctors ($P = 0.141$), or the cost of Western medications ($P = 0.777$). The only significant demographic characteristic found was gender, as boys were more likely to see a TCM practitioner than girls ($P < 0.001$).

Despite the predominant reliance on Western medicine for illnesses in the past 3 months, Lau et al. concluded that there was a popular demand for TCM practitioners amongst Hong Kong adolescents. Given the lack of strict oversight of these TCM clinics and practitioners, the authors suggested the need to further standardize and regulate the practice of TCM. Furthermore, the need exists to elucidate the potential negative interactions between TCM and Western medicine as well as the reasons that drive adolescents to seek both types of medical care.

The authors concede the importance of distinguishing between adolescent and adult health needs and behaviors. Given the large influence that Western cultures has on the youth culture of Hong Kong, we expect that adults would have a greater tendency to seek medical care from TCM practitioners. Thus, it is important to not over-generalize Lau et al.'s findings to the whole population, especially given the fact that this study was done on adolescents while most other similar studies have only involved adults. Nevertheless, the study pointed out some of the important patient characteristics to consider when examining the usage patterns of TCM as well as provided a useful prevalence rate in one subgroup of the population.

The general perception among the Hong Kong population is that Western medicine and TCM are complementary, rather than contradictory (Lee, 1983). Or, as the Lau et al. study suggested, patients may be driven to TCM because they seek assistance with certain maladies pertinent to TCM care. Donnan et al. found that patients largely saw TCM practitioners as specialists for injuries and skin diseases (1991).

The term “doctor shopping” refers to the consultation of both Western physicians and TCM practitioners for the same disease. This phenomenon was exhibited by 12.1% of adolescents in the Lau et al. study (2001). Although Lo et al. reported that most patients perceive Western medicines to be more effective than TCM, the prevalence of “doctor-shopping” was found to be approximately 35-40% among Hong Kong adults, mostly attributable to patient complaints of the persistence of disease symptoms.

In 1994, Lo et al. suggested a number of reasons for the prevalence of Hong Kong patients seeking both Western and TCM medical advice for the same illness. The authors conjectured that growing emphasis on patient rights, medical consumerism, and patients' desires to be active in the healthcare decision-making were all reasons to

account for this rate of doctor shopping. The authors also suggested that patients desire to seek out the highest quality of care available, instead of simply relying on the first medical practitioners they have contact with.

The Lo et al. study was based on information gathered from the then 64 public clinics in Hong Kong also known as Government Outpatient Departments (GOPDs). These government-operated and subsidized clinics charged significantly less than private ones. The samples were comprised of two systematic selections of GOPD patients chosen in 1989 and 1990. In 1989, 1387 patients were selected and 869 structured, face-to-face interviews were included in the study. In 1990, the 901 patients involved in the study had telephone interviews.

Clinic patients involved in the study were asked about whether their personal habits of doctor shopping as well as their satisfaction regarding GOPD clinical visits, medical treatment received there, and their general patterns of healthcare utilization. Follow-up interviews were conducted at 6 and 12 months to inquire into any health conditions that developed in the interim.

Lo et al found a prevalence of doctor shopping of 38% (95% CI, 36 to 40%) in 1989 and 36% (95% CI, 33 to 39%) in 1990, but expected that these figures actually underestimated the true prevalence of the phenomenon. First, patients of the public GOPD clinics only comprised less than 20% of the Hong Kong population and were mostly less affluent citizens who could not afford to pursue other healthcare options outside of heavily government-subsidized care. Second, the study only looked at patients at one point in time seeking medical care for one illness episode and could thus not capture patients who might seek alternative care for other illnesses outside of the 6-12 month study time frame.

Patients most often cited the type of illness and the persistence of symptoms as reasons for doctor shopping. In the 1989 study, male doctor shoppers were more often middle-aged [OR=2.81 (1.17, 6.75)] or had chronic medical problems other than Diabetes Mellitus or Hypertension [OR=3.08 (1.18, 8.03)]. In comparison, females who doctor shopped were more likely to be younger, of age 20 to 39 years [OR=4.25 (1.91, 9.45)] but were more likely to present either for an acute illness other than DM or HTN [OR=2.12 (1.17, 3.86)] or a chronic health problem [OR=2.12 (1.07, 4.18)].

Results differed slightly in the 1990 study. In male participants, the type of illness was still a predictor for doctor shopping, which males were more likely to do for both acute [OR=9.03 (1.44, 56.62)] or chronic problems [OR=10.84 (2.05, 57.35)]. In contrast, doctor shopping by females was predicted by their perceptions and expectations of healthcare. Female patients were likely to be doctor shoppers if they were dissatisfied with the healthcare services they received at the GOPD [OR=2.62 (1.14, 6.00)], expected extensive communication with their physicians [OR=2.92

(1.24, 6.92)] or believed that, if offered, an injection would hasten their recovery [OR=2.95 (1.40, 6.22)].

These differences found by Lo et al may originate from sex-based healthcare differences as well as the gender environment in Hong Kong. Psychological research done shortly before this study reported that Chinese men had historically been taught to consider themselves the stronger sex and to be stoic in matters related to health. Social norms also dictated that men their emotions (Kwong and Wong, 1981). Thus, these gender norms may have lead to the differences in how men and women interacted with the healthcare system. It would be interesting to learn how these gender norms persist in contemporary Hong Kong and how much they continue to affect the health-seeking behaviors of men and women. These disparities could be useful in understanding the healthcare behaviors of the largely male HIV+ patient population of Hong Kong.

Lo et al. also asked patients to report their reasons for doctor shopping. The most common reason given in both years was the persistence of symptoms; 69% in 1989 and 75% in 1990. Unfortunately, one acknowledged weakness of the questionnaire was its ambiguity in querying how long after the onset of symptoms and after seeking one type of medical care that patients waited before seeking a second type of medical care. What is considered a long time for symptoms to persist certainly varies by patient and the severity and nature of symptoms.

Patients' interactions with and perceptions of Western medical care also influenced how often they also sought TCM care. Doctor shopping patients also reported: a lack of trust in Western physicians or medicine (16% in 1989, 4% in 1990), the inconvenience or unavailability of services at GOPD (7%, 6%), not liking the attitude of their Western physicians at their last GOPD clinic visit (2%, 4%), and the cost of care of GOPD (2%, 9%). These findings were not surprising, as patients who were somehow unsatisfied with or wary of Western medical care should have been more likely to seek other forms of medical treatment.

Studies such as our and that of Lo et al highlight the importance of understanding patient health behaviors, as the risk combining two medical practices can be dangerous, not to mention costly. Doctor shopping patients are at risk of unfavorable outcomes when the two practitioners have no knowledge that the patient is concurrently seeking the medical recommendations of the other. Such patients are at risk for negative drug interactions or being advised to avoid the potentially beneficial treatments of one practitioner.

Lo et al postulated the male patients with DM and HTN in the 1989 group were unlikely to doctor shop was because these patients were likely elderly men who were returning to the GOPD mostly for medication refills and probably had already

accepted the level of care they received there. Thus, these patients were unlikely to have the motivation or financial means to seek care outside of the GOPD, such TCM care. Other elderly patients with such chronic health problems who were unhappy with the GOPD care had likely stopping attending the GOPDs already and were therefore not included in the study.

In contrast, doctor shopping patients that did not have HTN or DM were likely younger than non-doctor shoppers. The authors suggested that these patients were more demanding of the quality of care they received and had more disposable income to be able to afford to shop around for other forms of care. Doctor shoppers may also have had unrealistically high expectations of the speed and effectiveness of Western medicine, a reason for why so many doctor shoppers expected that an injection might accelerate their recovery. The results of this study highlight the importance of finding the personal characteristics that differentiate how patients from different demographic categories interact with the Hong Kong medical system.

One weakness of the Lo et al study is that the authors did not ask patients to describe the specifics of their doctor shopping behavior. For instance, it was unclear whether patients had begun with Western care and then turned to TCM, or vice-versa. Patients were also not asked whether they had seen more than one Western physician, another type of doctor shopping. Moreover, patients were not asked just how much seeking TCM medical advice had affected the treatments offered by Western physicians. Had patients ever taken an herb or medication provided by a TCM practitioner? Had a TCM practitioner ever advised a patient to discontinue treatment or care by a Western physician? Unfortunately, it was unclear just how much visiting a TCM practitioner had affected the care that these patients received at the GOPD clinics.

Furthermore, the authors failed to provide explanations for the, at times, wide variations between the 1989 and 1990 questionnaires. As one year is not a significant period of time, the differences between the two studies call into question the generalizability of their results.

Nevertheless, the study is useful for calling attention to the phenomenon of patients accessing both Western and TCM medical care and the need to gain a more thorough understanding of how these interactions may affect patient care from both sources.

Clearly, the integration of Western and TCM health systems has critical implications for healthcare outcomes – especially for those patients with long-term healthcare needs, such as HIV/AIDS patients. While the benefits remain unclear, the disadvantages such as discontinuity of care, misunderstandings and misconceptions between practitioners, and negative drug interactions are causes for concern.

The aim of this study was to further examine a healthcare environment where two divergent systems of healthcare coexist. Our study intended to answer four questions regarding how our patients navigate both medical systems when seeking medical care.

- (1) Does the use of TCM by ethnic Chinese male HIV patients have any relation to adherence to HAART?

Clinical and virologic outcomes suffer when patients are inappropriately treated with anti-retrovirals to which they are resistant or when they have poor adherence. Yet, due to the cost, burden of complicated drug regimens, and plethora of devastating side effects, adherence is often a complicating factor in the treatment of AIDS patients. Patients with poor adherence have been found to have double the rates of virologic rebound after just 4 months of treatment (Le Moing et al, 2002). Unfortunately, adherence research has been hampered by the lack of a gold standard method of measurement. A landmark study by Paterson et al. in 2000 provided the 95% adherence benchmark, which is often cited as the goal for treatment (2002)

Paterson et al's study was conducted at two HIV clinics in Veterans Affairs Medical Centers in Pittsburgh, Pennsylvania and Omaha, Nebraska. For 3 years, consecutive HIV+ patients of the VA primary care clinics were enrolled; both those already being treated with protease inhibitors ("experienced" patients) and those who were just beginning to take protease inhibitors ("naïve" patients) during the study's duration.

Upon enrollment, each patient received a thorough medical history that included: demographics, medical history, medication use, use of illegal or non-prescription substances, alcohol abuse, adherence strategies, depression, a General Health Questionnaire, and patient's beliefs on the relations between adherence and longevity. Further, each patients' physicians and clinic nurses were asked to predict whether each patient had greater than 80% adherence to anti-retroviral medications.

During the study, at 3 month intervals, participants were asked whether there were any changes in: employment, use of alcohol or illegal drugs, residence, attribution of symptoms to the anti-retroviral therapy or HIV infection, or medication. They were also screened for depression, general health and any opportunistic infections that may have developed. In addition to baseline tests, patient also had HIV RNA levels (Roche Amplicor System) and CD₄ lymphocyte subpopulation assays lab tests every 3 months.

To measure adherence, each patient was given a Medication Events Monitoring System (MEMS TrackCap), consisting of a standard medication bottle with a pressure-activated micro-processor in the cap to record the date, time, and duration of

each bottle opening. Patients were given one bottle with a micro-processor cap for each prescribed protease inhibitor. Although the system could not guarantee that medication was consumed with each opening, the authors were confident that the patients were not likely to have engaged in significant deception of researchers for long periods of time. To record the results, the bottles were scanned at each HIV clinic visit.

Adherence rate was defined as the number of doses recorded by the MEMS TrackCap divided by the total number of prescribed doses during the monitoring period. Timing of doses was also correlated to the intervals of bottle openings to ensure proper dosing frequency.

Virologic failure was defined as a HIV RNA level of >400 copies/mL. CD₄ lymphocyte counts were also compared between clinic visits. Opportunistic infections, hospitalizations, and all-cause mortality were also recorded.

Over the study's 1.5 year duration, 99 patients were unrolled. Of those, 6 withdrew and 12 did not return the MEMS TrackCaps, leaving 81 patients with complete clinical data. The mean duration of follow-up was 6 months (range 3-15 months). Overall adherence for the entire 81 patients was 74.7% (33,894 doses taken out of 45,397 prescribed).

As expected, the degree of adherence was significantly associated with virologic failure (relative risk, 0.97 [CI 0.96 to 0.98], $P=0.001$). Virologic failure rates increased as adherence fell. Of the 23 patients with $>95\%$ adherence, only 5 (22%) had virologic failure. Meanwhile, the virologic failure for patients with 80-94.9% adherence was 61% (OR, 5.6 [CI, 1.3 to 25.7]) and 80% for patients with less than 80% adherence (OR, 14.4 [CI, 3.4 to 66.6]).

Detectable viral loads also decreased with greater adherence, regardless of a patient's baseline. In patients with baseline HIV RNA levels <400 copies/mL, 0 of the 7 patients with adherence $>85\%$ had detectable HIV RNA levels at the final visit, in contrast with 7 out of 17 (41%) of patient with less than 95% adherence. Meanwhile, amongst patients with baseline HIV RNA levels >400 copies/mL, 5 of 16 (31%) with adherence $>95\%$ had detectable HIV RNA levels at the final visit, compared to 35 of 41 (85%) with adherence less than 95%.

Increases in CD₄ lymphocyte counts were also associated with degree of adherence ($P=0.006$, $R=0.31$). Participants with $>95\%$ adherence had a mean increase of 83 cells/mm³, while those with less than 95% adherence only had a mean increase of 6 cells/mm³. The relationship was still significant when results were controlled for length of follow-up.

Three episodes of AIDS-defining infections all occurred in patients that had $<95\%$ adherence. Patients with $<95\%$ adherence also had significantly more mean

days of hospitalization per 1000 days of follow-up; 12.9 (range 10.8 to 15.9) versus 2.6 days (range, 15 to 4.3) [$P < 0.001$].

Paterson et al. reported that patients with $>95\%$ adherence were more white ($P=0.0017$), had a higher monthly income ($P=0.058$), and had lower psychiatric morbidity, per the General Health Questionnaire ($P=0.0014$). When compared to those with $<95\%$ adherence, patients with $>95\%$ adherence had been infected with HIV for a greater length of time (mean duration of infection, 8 vs. 6 years, $P=0.12$). Furthermore, only 1 of 23 (4%) of patients with $>95\%$ adherence had problems with alcohol abuse, compared to 10 of 58 (17%) of patients with $<95\%$ adherence.

Factors found not to be associated with $>95\%$ adherence included: sex, HIV risk factors, employment, or accommodation status. Interestingly, neither the attribution of symptoms to HIV infection or to anti-retroviral therapy, nor the use of a timer or alarm as reminders for medicating were associated with $>95\%$ adherence. ($P>0.2$).

Paterson et al. also found that twice-a-day drug regimens had a non-significant improvement in adherence (mean adherence, 89.2%) compared to three-times-a-day regimens (mean adherence, 85.7%, $P = 0.09$). None of the 7 protease inhibitors had a significantly better rate of adherence.

Clinic physicians were worse than nurses at predicting whether patients would have good adherence. Physicians wrongly predicted 41% of their patients whereas nurses missed only 30%; but the difference was not significant [OR, 1.8 [CI, 0.8 to 4.0]; $P = 0.12$). Although seemingly asinine, this phenomenon can be crucial to patient care, as physicians may be hesitant to prescribe anti-retroviral to patients that they do not expect to take their medication as prescribed. Also, physicians may falsely alter regimens for patients who they assume are failing therapy but might actually just be non-adherent to their medication.

Overall, Paterson et al.'s result support that patients with $>95\%$ adherence had improved virologic outcomes, higher increases in CD₄ lymphocyte counts, and lower rates of hospitalization. The study was a landmark for dispelling the convention that 80% was an acceptable adherence for the treatment of chronic illness and questioning the utility of simply asking patients how many doses that had missed in the past few days as an accurate gauge of adherence.

Of course, the question remains as to the accuracy of patient self-report of adherence, especially compared to other possible surrogate markers of adherence. In 1998, Walsh et al. claimed that patient self-report is a easy and economical method of assessing anti-retroviral adherence (Walsh et al, 1998). In 2001, Duong et. al. carried out a prospective, cross-sectional study comparing 3 markers of adherence—patient self-report, Protease Inhibitor (PI) levels, and biologic parameters associated with anti-retroviral drugs—and their relationships to virologic response.

Previously, drug adherence had been detected by trough plasma levels of dideoxynucleosides as a parameter of medication use in clinical trials (Kastrissios et al., 1998), among others. Similarly, the reported association between low plasma PI concentrations and virologic failure also suggested its utility as a marker of drug adherence (Lorenzi et al, 1997).

The comparison study was comprised of 149 HIV+ patients at the Dijon Hospital AIDS outpatient clinic. All patients, symptomatic or not, were eligible if their drug regimens included at least one PI; usually with 2 nucleoside analogs and 1 or a combination of PIs (indinavir, saquinavir, nelfinavir, or ritonavir) for 4 weeks or more. Patients receiving non-nucleoside analogues were excluded. Each patient had 2 blood samples drawn—one for CD₄ count and viral load, and another for plasma PI levels. Nursing staff recorded the time of blood drawing as well as the time of the last PI administration, as reported by patients. Each patient then completed a Patient Medication Adherence Questionnaire (PMAQ), which was a 31 question, self-administered evaluation of drug adherence. The PMAQ asked patients about their estimated proportion of prescribed doses taken over the past 4 weeks, as well as their general adherence behavior.

Treatment efficacy was measured by plasma HIV RNA levels (Ultra Sensitive HIV-1 Amplicor Monitor Assay) which was sensitive for as few as 20 copies/mL. Virologic response compared baseline HIV RNA levels at beginning of treatment to levels at time of study enrollment. Positive virologic response was defined as a decrease greater than or equal to 2 log₁₀ copies/ml HIV RNA in first time PI-treated patients, and a decrease greater than to 1 log₁₀ copies/mL for patients who had previously been treated by at least one other PI.

Patients who did not have virologic response but normal plasma PI concentrations had analyses for the HIV protease gene. The test involved viral RNA extraction (QIAAmp viral RNA kit, Qiagen), amplification by reverse-transcription PCR followed by nested PCR, and then sequence analysis by direct sequencing (ABI Prism BigDye Terminator Cycle Sequencing Ready Reaction kit) utilizing Sequence Navigator software (Nijhuis et al, 1998).

Plasma PI levels were determined by various methods involving ultraviolet detection, depending on the type of PI. Per time of last ingestion as reported by patients, concentrations were compared to expected levels derived from 24hr pharmacokinetic profiles in healthy volunteers. To control for individual variations in drug levels even seen in healthy volunteers, the range of expected drug levels was widened to include values at least one half of the expected level. Thus, non-adherence was defined as having a ratio less than 0.5 of the concentration level found in the study in comparison to the expected level for that time interval.

The study population of 149 patients had an average age of 40 years; most of whom, 104 (70%), were male. The patients were at various CDC 1993 Criteria clinical stages: 60 patients were Stage A, 49 Stage B, and 40 Stage C. The mean baseline CD₄ count was 485 ± 10^6 cells/L and HIV RNA level baseline was 4.6 log₁₀ copies/mL (no SD given for either). Only 14 (9%) were on their first PI regimen, while 93 patients (63%) patients had previously been treated with another PI. The most commonly prescribed PI was nelfinavir, which was given to 47 (31%) patients, mostly as a single PI. Another PI, saquinavir, was mostly prescribed in combination with other PIs—22 patients with ritonavir and 11 patients with nelfinavir.

In total, 112 patients (75%) had a virologic response and 37 patients (25%) had virologic failure. Virologic failure was proportionately more common in PI-naïve patients (49 of 56 patients, 88%) as compared to patients who had previously been treated with a PI (63 of 93, 68%) [$P=.01$]. Yet, no difference was found in virologic response in patients taking different PI regimens.

Of the total 149 patients, 122 patients (81.8%) had trough plasma levels greater than reference values, while 27 patients (17.9%) had lower levels. Trough plasma levels were significantly associated with virologic response ($P<0.0001$). In matching PI levels and virologic outcomes, 117 (78.5%) patients had concordant measures: 101 patients had virologic responses and normal PI levels while 16 patients had virologic failure and low PI levels. Meanwhile, 32 (21.5%) patients had discordant measures. Virologic failure but normal PI was found in 21 patients. Fourteen of such patients had HIV protease genotype studies, of which 12 had mutations for PI resistance. Also, 11 patients were found with virologic response but low PI levels.

When Duong et al compared the patient responses to the Patient Medication Adherence Questionnaire (PMAQ) to virology response, they found 4 items on the PMAQ to significantly associated with virologic response. The 4 responses were: “I have not missed any doses of PIs over the last 4 days” ($r=0.18$, $P=0.03$); “I have not missed taking all the pills at least 1 day over the last 4 days” ($r=0.22$, $P=0.005$); “Most of the time, I have followed the special instructions associated with the anti-retroviral medications over the last 4 days” ($r=0.15$, $P=0.03$); and “I have had a medication adherence of $>80\%$ over the last 4 weeks” ($r=0.33$, $P=0.001$).

Using these 4 items, the authors created a 4-point adherence score. Adherence was defined as a maximum score of 4 points, while non-adherence was any score <4 points. One hundred (67%) of the 149 patients had maximum scores while 39 (33%) patients had lower scores revealing a significant correlation between adherence score and virologic response ($P=0.001$). Thus, the utility of the adherence score to predict virologic response had a sensitivity of 74%, specificity of 54%, positive predictive value of 83%, and negative predictive value of 40%. Of course, this score, like all

self-report measurement lacked any scientific way to gauge a patients' reliability as a historians or their innate desire to please healthcare workers by over-estimating adherence.

While the authors purported that their 4 question adherence score can capture both short and long-term adherence behaviors, the brevity of their questionnaire coupled with the one-time PI sampling leaves their results vulnerable to scrutiny regarding how accurately these samplings can assess a patients' chronic behaviors following complex and demanding drug regimens.

Nevertheless, the authors did find a very strong association between virologic failure and maximum adherence scores. Still, because of the low predictive negative value of the study, the adherence score seems only to have utility for detecting adherence in patients who answer all 4 adherence-related questions positively.

Results varied among biologic parameters of medication use. Thirty patients (21%) took didanosine, but only 3 (9%) had uric acid levels that were higher than the reference range. Of the 35 patients on Indinavir, 8 (23%) had elevated levels of bilirubin. No significant association was found between virologic response and either uric acid ($P=0.75$) or bilirubin ($P=0.32$). However, in the 60 (40%) patients treated with zidovudine and 86 (58%) patients treated with stavudine, macrocytosis was seen in 131 (90%) of these patients. Thus, for patients taking zidovudine or stavudine, there was a significant association between macrocytosis and virologic response ($P=0.004$).

Multivariate analysis was conducted for the 146 patients receiving zidovudine or stavudine to examine the relationship between self-reported adherence, PI level, and macrocytosis, with virologic response as the dependent variable. Overall, the authors found that PI level was the strongest significant predictor of virologic response (adjusted OR, 6.4; [95% CI, 2.3 to 17.3], $P=0.003$). Also found to be independent factors of virologic responses were self-reported adherence (OR 2.9; [95% CI, 1.2 to 71], $P=0.01$) and macrocytosis (OR, 3.5; [95% CI, 0.9 to 12]; $P=0.5$).

Although the Duong et al. study clearly reinforced the importance of adherence for HIV viral suppression, they also acknowledged two clear limitations to their study. First, in patients who are not naïve to PI therapy, virologic failure is not considered a reliable marker of adherence. Since such a large proportion of these patients had previously been treated with PIs, it is uncertain that the virologic failure was not due to factors such as viral genotype mutations. The authors tried to limit this weakness by selecting a less rigorous cutoff for virologic failure to offset the higher probability of partial response in PI-experienced patients. Second, as PIs have short half-lives, the trough concentration can only reflect a dose of medication taken the day before. Thus, while this cannot be a true gauge of long-term adherence, the authors cited several

studies supporting that recording doses taken over the past 4-7 days could be a dependable indicator of long-term adherence (Eldred et al 1998 and Hecht et al 1998).

Moreover, Duong et al demonstrated that, as a marker for drug consumption, PI level can significantly predict virologic outcome thus connecting poor adherence to virologic failure. Yet, the authors note that trough levels can vary depending on individual pharmacokinetic properties. A similar study revealed that when single time point measurements are used to estimate drug exposure, patients with lower exposure to nelfinavir and saquinavir had lower clearance rates of HIV-1 RNA (Hoetelmanns et al, 1998). Thus, despite individual differences in metabolism and response, PI levels can be useful markers for drug adherence. Nonetheless, these findings intimate the possible utility of assessing individual pharmacokinetic characteristics to adjust dosages and drug regimens to improve therapeutic benefit.

The majority of patients with normal PI levels but still with virologic failure had viral gene mutations suggestive of drug resistance, rather than non-adherence. Yet, the authors suggest non-adherence explain the 2 patients with virologic failure despite normal drug levels. The authors posit that these patients might have poor adherence at baseline but may have taken their medications just prior to the clinic visit; a “toothbrush effect,” which is common in adherence studies. Duong et al ascribe the finding of 11 patients with virologic response but low PI levels to either these patients having missed their last PI dose or to a sampling error due to errors due to incorrect reporting of time interval from last dose, blood sampling inaccuracy, or poor drug absorption. Yet, the authors fail to take into the account the possibility that patients have virologic response despite non-adherence.

Duong et al’s results showed little evidence supporting the utility of biologic parameters as markers of drug consumption. Previous studies had linked indinavir to elevated bilirubin levels (Maserati et al, 1998) and didanosine to elevated uric acid (Richardson et al, 1993). Duong et al’s results did not confirm either of these findings, which may have been the result of lower doses of medications used. The only measure found in this study to be significantly associated with drug adherence was macrocytosis, which has also been supported by other studies (including Ahmad and Sukthankar, 1997). While macrocytosis appeals as a cost-effective marker of long-term adherence, its lack of specificity is obvious in light of the multitude of unrelated causes of increased Mean Corpuscular Volume (MCV), such as: deficiencies of vitamin B12 and folate, alcoholism, or liver disease. In addition, because of the time frame required for a patient to develop macrocytosis, an increased MCV may still be seen when a patient has missed recent doses despite prior adherence.

Duong et al conclude by suggesting a two-tiered method to measure adherence by coupling patient self-report with plasma anti-retroviral drug levels. While PI plasma

levels had the strongest association with virologic failure, its everyday use is not yet a practical consideration for most clinics considering the ease and low cost of simple patient questioning. As their results supported its strong positive predictive value, self-report could be reliably used as a first-line assessment while the measurement of plasma PI levels would only be indicated in patients with questionable adherence. Yet, patient self-report is nonetheless supported by both Duong et al and Paterson et al a reliable, yet imperfect and imprecise, marker for patient adherence to anti-retroviral medication, when adherence is defined as virologic suppression.

Given the complexity of HAART regimens, we hypothesized that the increased burden of also taking any forms of TCM would lead TCM-using patients to display lower levels of HAART adherence in comparison to non-TCM using patients.

(2) How prevalent is TCM use among HIV-infected Chinese patients?

At the time of this study, no previous investigation had been conducted concerning the use of TCM by HIV patients in Hong Kong. One review of studies of use of Complementary and Alternative Medicines (CAM)—including TCM among many others—by HIV/AIDS patients in several Western nations found prevalence rates ranging from 27%-100% (Ernst, 1997). According to our research, the only previous study of Asian HIV/AIDS patients was conducted in Thailand in 2003 and reported that 95% of HIV patients has used some form of CAM and that 78% had visited a CAM provider (Wiwanitkit, 2003). These wide variances suggest that ethnic and cultural factors, in addition to study methods, play a part in determining use of CAM and TCM.

The Wiwanitkit study involved interviews of 160 HIV+ patients at the Out-Patient Division, King Chulalongkorn Memorial Hospital in Bangkok, Thailand. Patients were asked about their use of vitamins, herbal therapies, dietary supplements, off-label prescription medication, and any other supplements used in the past year. Patients were also directly asked whether they had visited an acupuncturist, herbalist, massage therapist, or other CAM provider in the past year. The interviewers were instructed to not use the term “alternative” at any time, to avoid any negative connotations that may be associated with the term.

Amazingly, 153 (95%) of the 160 of participants had used CAM in the past year while 124 (78%) had visited a CAM provider. Most patients had used more than one form of CAM (mean 2.4, SD 1.5). The most common forms were: ritual remedy from Buddhist temple (n=128, 84.2%), biophysical approach (n=102, 67.1%), Thai traditional herb remedy (n=84, 55.3%), vitamin supplement (n=78, 51.3%), dietary supplement (n=54, 35.5%), fold remedy (n=28, 18.4%), off-label prescription medications (n=22, 14.5%), massage (n=15, 9.9%), and superstitious remedy (n=11,

7.2%). Yet, despite these impressive rates of CAM use, patients still visited their primary care physicians more often than CAM providers, 12 visits per year versus 4.

Wiwanitkit ascribed the high rate of CAM usage in his study population to the Asian cultural values and traditional treatment traditions in Bangkok. As this is the only known study to look at CAM/TCM use in an Asian HIV+ population, it suggests that we will find a higher rate of usage in Hong Kong than a comparable Western population.

In order to gain a deeper understanding of the usage of TCM by HIV/AIDS patients in our research setting, we raised the following questions:

- (3) What types of TCM are used by this population?
- (4) What are the predictors of TCM use in this population?

HIV/AIDS in Hong Kong

As of August 16, 2005, there were 2,647 HIV cases in Hong Kong Special Administrative Region of which 743 had progressed to AIDS. Of all cases in HKSAR, 80% were male patients and 69% were ethnic Chinese. While the most common means of transmission was heterosexual contact, cases due to injection drug-use and homosexual contact were on the rise (Press Meeting given by Dr. Ho Lei-Ming, Department of Health).

Government-subsidized clinical care for Hong Kong patients with HIV/AIDS who elect to enroll is offered at the Integrated Treatment Centre (ITC) and Queen Elizabeth Hospital by the HKSAR Department of Health. ITC has an active caseload of 823 patients with HIV/AIDS, nearly 1/3 of all HIV/AIDS cases in HKSAR. Of those, 82% are male and 82% are ethnic Chinese.

One of this study's collaborators had previously investigated adherence within the ITC HIV/AIDS clinic population to examine the effectiveness of the ITC's unique drug adherence counseling program (Fong et al, 2003). Since 1997, ITC patient care has been focused on the preparation, support, and monitoring of patients taking anti-retroviral medications. Specifically, nurse assess and individually counsel each patient regarding knowledge of drug regimen such as ability to identify medications and dosage; drug-taking behaviors, and possible barriers to adherence. Also, at each visit, nurses ask patients about missed doses and keep track of adherence.

In the Fong et al study, patients were selected that where Chinese, had been on HAART for >12 months and had undetectable viral loads. The study involved a retrospective analysis of patient records focusing on six factors that might have impacted HAART adherence: sociodemographic characteristics, HIV disease status,

anti-retroviral therapy, and drug adherence. The researchers also correlated each patient's last assessment of knowledge of their anti-retroviral regimen with their viral load (measured by PCR, Amplicor Monitor Assay).

Fong et al's study included 161 eligible Chinese patients of the ITC, of which most were male ($n=142$, 88.2%) and single ($n=99$, 61.5%). The average age was 41.1 years old (range 27 to 73) and more than 25% had been diagnosed HIV+ for >5 years.

Many patients had notably burdensome drug regimens. Of the 161 participants, 81 (85.7%) were on Protease Inhibitors, 100 (62.1%) had a daily pill burden over 10, 123 (76.4%) required taking pills three times a day, and 86 (53.4%) required meal restrictions.

Patient adherence was classified by full (Grade A) and partial (Grades B to D) adherence. Overall, 130 (80.7%) patients had full adherence and 135 (83.9%) had undetectable viral loads (per this study, <500 copies/mL). Patients with full adherence were four times as likely to have undetectable viral loads ($n=115$, 85.5%) in comparison with patients with partial adherence ($n=20$, 64.5%). Thus, full adherence had 85% sensitivity for undetectable viral load and a positive predictive value of 89%.

By univariate analysis, no demographic factors were significantly associated with drug adherence; nor were HIV disease status or characteristics of anti-retroviral therapy. Persistent gastrointestinal complaints such as epigastric discomfort, nausea, or vomiting were non-significantly associated with poorer adherence ($P=0.03$). The only factors found to be significantly associated with poorer adherence were psychosocial barriers such as forgetfulness and busy work load, and irregular clinic follow-up in the form of missed appointments ($P<0.001$ for each). By multivariate analysis, these 3 factors remained independent risk factors for poorer adherence: missed appointments (adjusted OR, 3.13; 95% CI 1.23 to 8.33), forgetfulness (adjusted OR, 4.55; 95% CI 1.64 to 12.5), and busy workload (adjusted OR, 6.67; 95% CI 1.75 to 25).

The high rate of full adherence (80.7%) found by Fong et al. is significantly higher than similar studies that found rates by self-report of 42%-62% (Gordillo et al, 1999 and Bangsberg et al, 2000). The authors suggest that these results support the usefulness and benefit of their individualized drug adherence counseling program. Yet, that Fong et al. were able to show such a strong correlation between self-reported adherence and viral load is a good indicator of the validity of the results. Moreover, Fong et al's study further supports Paterson et al's finding discussed that viral suppression drops precipitously when patients have <95% adherence.

The focus of the Fong et al. study was to examine the factors were associated with poor adherence. However, their analysis may have been statistically hindered by the generally high rates of adherence found among the ITC patients. Previous studies

had found that a great number of medications (Kleeberger et al, 2001) and dosing more than three times per day (Eldred et al, 1998) were both associated with lower adherence. Yet, in this study, no aspects of the drug regimen were related to incomplete adherence despite the seemingly demanding regimens of most of the study participants. Again, the authors speculated that the ITC's counseling program may have had a role in supporting patients and helping them cope with such demands. Also, the authors suggested that Chinese patients are more likely to follow doctors' orders.

The relationship between poor adherence and missing follow-up appointments had been reported in a previous study as well (Valdez et al, 1999). Thus, if drug adherence is not measured, missing appointments could be a surrogate for patients with non-optimal adherence. If not all patients can receive personal counseling, than patients who regularly miss appointments would seem the ideal ones to target for counseling and re-evaluation of treatment.

Forgetfulness and busy workload as obstacles to full adherence have similarly been observed in prior studies (Le Moing et al, 2002 and Chesney et al, 2000). These findings reinforce the need for healthcare providers to work with patients and understand their individual lives and needs to personally tailor drug regimens. Also, it was a reminder of the factors outside of the direct control of physicians and nurses that may affect adherence; but ones that nevertheless may be ameliorated by intensive and personalized counseling.

There were several limitations to the Fong et al study recognized by the authors. First, it was a retrospective study with adherence data retrieved from clinic records. Second, the interviews did not involve a structured set of questions and were often crammed into the patients' schedules as time would permit. Third, multiple interviewers were involved, thus creating an uncertain level of intra-observer bias. Fourth, while the study focused on factors that lowered adherence, it did not pay attention to factors that might augment it. These beneficial factors would be especially useful to study to better understand the high adherence found at the ITC. Fifth, adherence was only measured by self-report of number of missed doses. How and when doses are taken are also important determinants of efficacy.

The Fong et al study established a strong precedent of adherence research at ITC. With their results, we were confident that patient population was adequately committed not only to personal well-being, but also to research. Moreover, we knew that as a result of the drug counseling program, the nursing staff had personal relationships with all patients. Using the Fong et al study as a template, we tried our best to both learn from and contribute to their previous work.

Study Population

For this study, eligible patients were ethnic Chinese and who had been on HAART for more than one year. As HIV/AIDS treatment is a long-term issue, so we focused on patients who had been on HAART long enough to display long-lasting patterns of usage. During the study's 5 weeks of administration (July 20, 2005 – Aug 17, 2005) 220 patients that fit the study's inclusion criteria visited the clinic.

In total, 85 questionnaires were completed, of which 81 were included in the results for analysis. As only 3 female patients completed the questionnaire, for the sake of precision, we limited the study to the male population. Although 18% of ITC patients are female, many of those female patients did not fit the inclusion criterion of being ethnic Chinese. Many of the individuals comprising the ITC's female patient population come from Thailand, India, Indonesia, and the Philippines while a greater percentage of the male patient population is ethnic Chinese. In addition, one patient did not complete the questionnaire so his questionnaire's results were discarded. In the end, the study we analyzed the results of the questionnaires completed by 81 male, ethnic Chinese HIV-positive patients at the ITC who had been on HAART for at least one year.

The average age of participants was 44.2 years (range: 20-72 years, SD=12.1). Forty four (55%) of patients reported working full-time, 16 (20%) were unemployed, 8 (10%) worked part-time, and 7 (9%) were retired. According to patient laboratory results measured on the same day as each patients' study participation, CD₄ counts ranged from 27-1358 / μ L although the average was 447 / μ L (SD=238). This broad range demonstrates that patients from a spectrum of disease stages were included in the study.

With the exception of one patient, all participants had an RNA viral load of <400 /mL. The single exceptional patient had a viral load of 54000 /mL. Review of his medical records by ITC nurses revealed that the patient been withheld HAART treatment for a 5-month "washout" period preceding the study due to his negative response to a previous regimen.

Adherence, according to patient self-report to ITC staff, was classified into 4 grades, as the ratio based on dividing the number of missed doses by the total number of doses that should have been taken since the patients' last clinic visit. Of study participants, 62 (77%) had Grade A adherence (100%), 18 (22%) had Grade B adherence (99-95%), and 1 (1%) had Grade D adherence (<90%).

Method

The study consisted of two components. The first was a series of interviews conducted by research staff to gain a better understanding of the ITC staff and patient population in order to create a more applicable and precise questionnaire. The second component was the self-administered questionnaire.

Part One: Interviews

The study began with a series of personal interviews aimed at gathering a basic understanding of HIV patient care and TCM usage among patients at ITC.

Face-to-face interviews were conducted of 7 patients, 2 spouses/relatives of patients, 4 ITC nurses, 1 ITC physician, 1 ITC social worker, and 1 TCM practitioner with no connections to ITC.

Patients were informed that for this study, TCM refers to the ingestion of proprietary preparation and/or herbal formulae (e.g. Chinese herbs, vitamins, dietary supplements, off-label prescription medications) or other forms of treatment (e.g. acupuncture*, massage, qi gong*) outside the scope of HAART.

Patients were asked to discuss current and past use of TCM, HAART adherence, quality of care at ITC, and their personal experiences with HIV/AIDS. In general, patients expressed overwhelming satisfaction with the care and support provided by ITC staff. Patients were grateful for the amount of time that ITC staff devoted to explaining the importance of full-adherence to HAART and all patients reported that their adherence was either 100% or close to it. The few cases of missed doses were attributed to forgetfulness, being too busy, or sleeping through a dose time. Most patients cited the importance of the scientific evidence and tangible proof of HAART in maintaining their CD₄ count as the main reasons for their high adherence.

Patient use of TCM ranged from none to multiple visits per week to TCM practitioners to purchase herbs for daily consumption. Those that used TCM only reported use of herbal teas, herbs prescribed by TCM practitioners, and over-the-counter (OTC) TCM medications/herbal preparations. Patients who received TCM prescriptions from TCM practitioners generally were given an assortment of 15-20 herbs to be prepared as a soup or tonic. Most TCM practitioners did not explain the contents and most patients did not know what herbs they were given. Except for one patient who began tai chi* after experiencing weakness in his legs after his HIV diagnosis, no patients interviewed used any other non-ingestible forms of TCM such as acupuncture, massage, or qi gong.

Most TCM-using patients had used TCM since childhood and were thus

accustomed to relying on it for their medical needs. Usually, TCM was not taken to directly treat HIV, but rather for minor illnesses- related to HAART or not – or for general health maintenance. Patients who did not use TCM reported visiting only Western physicians when ill.

Some patients had fully disclosed their HIV status to family and friends while others had told none. Those who had told their family and friends usually did so because they anticipated and subsequently received a great deal of support from their close relationships. Such support was very meaningful to patients, especially when partners/spouses, friends, or family would accompany patients to ITC clinic visits.

During the course of the interviews, ITC nurses, physicians, and staff estimated that 10% of patients used TCM. Staff would not deliberately ask patients about TCM usage, but if patients made inquiries about TCM use, the general rule was for staff to state their lack of training and expertise in these matters. Staff would only suggest that because some TCM medications may have negative interactions with HAART patients should try to separate taking HAART and any TCM by about 4 hours.

ITC staff explained the extensive educational and psychological preparations that patients were given before starting HAART for the first time. Patients were explained the importance of 100% adherence and that imperfect adherence might be more detrimental than not taking HAART at all. ITC physicians and nurses acknowledged some patients that do miss doses due to the emotional and psychological factors related to acceptance of disease and its lifelong consequences.

One TCM practitioner who had trained in Shanghai and now owned a private practice in Hong Kong was interviewed. She indicated that most TCM practitioners would not need to ask a patient directly about their HIV status in order to effectively treat the disease and its symptoms. The goal of TCM, she stated, was to treat the individual's entire well-being, not just a particular symptom or disease.

The TCM practitioner demonstrated how she would compile a list of 15-20 Chinese herbs as a prescription for patients to boil the herbs and drink the resulting tonic. Although practices varied between TCM practitioners, she would not often instruct patients to seek additional TCM-based care, such as acupuncture or cupping. She believed that patients with HIV/AIDS could be treated just as well if not better using only TCM practitioner-prescribed Chinese herbs than by using Western medications.

Our initial questionnaire was revised based on information gathered from these interviews. A pre-test was conducted with 10 patients to gauge patients' reactions and incorporate their comments regarding the questionnaire's length, readability, and applicability. Subsequently, the final version of the questionnaire was prepared.

Part Two: Questionnaire

Patient Recruitment

Daily appointment lists were screened for eligible patients. While in the seating area awaiting their appointments, eligible patients were approached by ITC nurses and informed that a study was being conducted in a separate room. If patients were willing, they could walk to the room to learn more about the study. Clinic nurses were relied upon for patient recruitment in order to respect patient privacy and avoid research staff intruding upon the patient waiting area.

Upon entering the study room, patients were greeted by the interviewer, a retired nurse who had worked previously at the ITC. A retired nurse was the ideal interviewer as she was familiar with the issues related to HIV/AIDS care but, at the same time, disconnected from current medical care received by patients. Thus, patients were assured sensitivity, discretion, and that the study would have no impact on their medical care.

Patients were given written and verbal explanations that the study concerned the possible use of TCM by patients on HAART. Patients were assured that their answers would remain anonymous and that their participation or lack thereof would have not affect the medical care received at ITC. They were informed that their medical records would be accessed by medical staff in order to obtain their most recent laboratory results, including viral load and CD₄ count. However, patients were reassured that no persons who do not already have ready access to their medical records, including research staff, would not be granted such access. Each patient that agreed to participate was given a Consent Form to sign and give their KB No. (patient identification no.).

Questionnaire Format

The questionnaire consisted of 4 sections:

1. TCM Usage

This section was only filled out by patients that had ever or were currently taking any form of TCM. Patients were presented separate lists of possible goals and reasons for taking TCM and also offered the opportunity to input any that were not included in the lists. Patients were asked about how often they consulted TCM practitioners and whether they informed their TCM practitioners about their HIV status. Patients were

asked where they had sought advice regarding TCM therapies. In addition, we inquired whether patients had discussed TCM usage with ITC staff and patients' level of comfort in doing so. We also wanted to know about patients' perceptions of ITC physicians' and nurses' views on TCM usage. Also, patients were given TCM usage charts to input the names of TCM therapies used and to describe their use of each form of TCM.

2. Perceptions of Western medicine and TCM

All patients were asked about their beliefs regarding TCM and Western medicine, including HAART. Patients were asked to compare the two in terms of: speed of effect, long-lasting effects, effectiveness in treating HIV/AIDS, effectiveness in treating HAART-related side effects, number of side effects, effectiveness in treating minor illness, effectiveness in treating major illness, and effectiveness for general health maintenance. In addition, we asked whether patients knew of any possible positive or negative interactions between TCM and HAART.

3. HAART adherence

All patients were asked to report their HAART regimen and the number of doses missed in the past month. Participants that missed at least one dose were presented a list of patient-related, drug-related, medical and social factors and prompted to indicate which may have contributed to missing doses. All patients were requested to indicate factors that encouraged them to adhere to HAART. Patients were also asked about level of trust in TCM and HAART, side effects experienced, and how much physical and emotional/psychological discomfort or pain that have experienced as a result of HIV/AIDS. Patients were asked whether they had ever sought treatment for alcohol, drug, or psychological problems.

4. Support

All patients were asked to report the amount of support received from ITC physicians and nurses, friends and family, and spouses/partners. Patients were also asked about how involved they wished to be in their own healthcare decision-making process.

Medical Chart Review

Non-research ITC staff were given the list matching each study participant's KB No. with Questionnaire No. Medical records were accessed for each KB No. and the following information was gathered: patient age, sex, and CD₄ count, viral load, and Adherence Grade from the most recent clinical visit.

Results

Patients were asked to specify which forms of TCM they used—if any—and to provide their basic patterns of usage. Overall, 50 (62%) patients reported having taken any form of TCM while 31 (38%) reported having never used any form of TCM. Based on responses, TCM-using patients were separated into Infrequent Users and Regular Users. Infrequent users were those that had reported using any TCM form only 1-2 times, such as patients who had sampled one form of TCM but had not used it habitually. Patients that reported both regular use of any form of TCM plus infrequent use of at least one other form of TCM were classified as Regular Users. Overall, 15 (16%) of all participants were Infrequent TCM Users and 36 (44.4%) were Regular Users. Among the 50 patients that had ever used any form of TCM, 13 (26%) were Infrequent Users while 36 (72%) were Regular Users (Table 1).

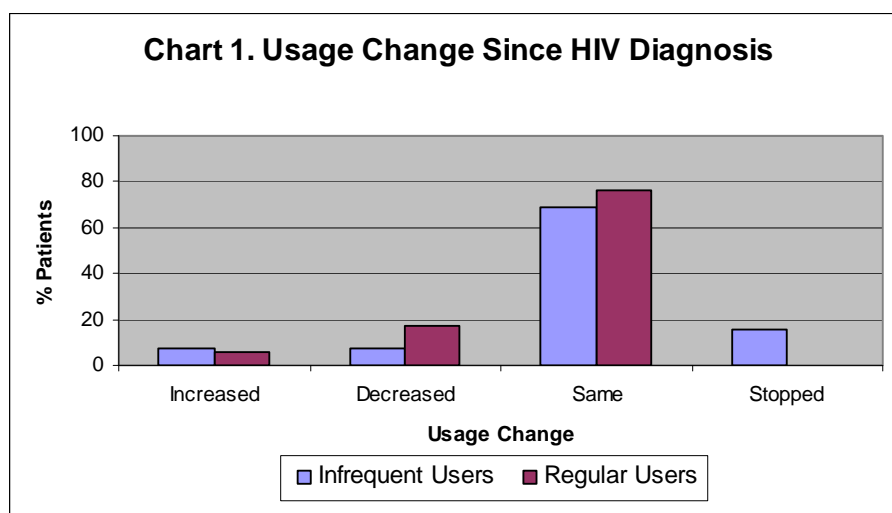
Table 1. *TCM Usage by HIV/AIDS Patients*

TCM Usage Type	No. Patients (N=81)	% of total patients
Non-TCM User	31	38%
<u>TCM-User (total)</u>	<u>50*</u>	<u>62%</u>
Regular	36	44%
Infrequent	13	16%

Prevalence of TCM usage among the study population. TCM-Users were categorized as Regular or Infrequent Users based on their usage patterns. In contrast to Regular Users, Infrequent Users only used TCM once or twice. One patient did not state whether he was a Regular or Infrequent User.

TCM-using patients were asked how their usage had changed since their diagnosis with HIV. No patients reported that his TCM usage had began only after

diagnosis with HIV. Among Infrequent Users (N=13): 9 (69.2%) reported that their usage pattern had not changed, 2 (15.4%) reported having stopped using TCM altogether, and 1 (7.7%) reported either increasing or decreasing their usage. Meanwhile, among Regular TCM Users (N=34): 26 (76.5%) reported no change in their TCM usage, 6 (17.6%) reported increasing their TCM usage, and 2 (5.9%) reported a decrease in use (Chart 1).



Questionnaires from the 50 patients that used TCM garnered 30 distinct forms of TCM being used (Table 2). All forms of TCM were ingestible and were either over-the-counter TCM preparations or herbs/herbal preparations prescribed by TCM practitioners. No patients reported usage of any form of non-ingestible form of TCM, such as acupuncture, qi gong, or massage. Of the 50 TCM-using patients, 33 (66%) used only one form of TCM, while 16 (32%) used more than one. One patient did not complete this section of the questionnaire. Of patients that used multiple forms of TCM, the average was 2.9 distinct types of TCM per patient (SD=1.2, range 2 to 6).

Table 2. List of *TCM used by patients*

Patients were asked to list any forms of TCM used, including: herbs, supplements, preparations, or techniques such as acupuncture or qi gong. Patients were allowed to list as many forms as desired. No patients reported using a non-ingestible form of TCM.

TCM Description	* No. Patients	Percent
<u>Prescription from TCM practitioner</u>	28	56%
<u>OTC Preparations (total)</u>	36	52%
Lingzhi*	12	24%

Cordyceps**	4	8%
<u>Other OTC Preps. (1 each)</u>	<u>20</u>	40%
	1	
<i>Wai geen</i>	1	
<i>Nu huang jue du pian</i>	1	
<i>Gee yee yum</i>	1	
<i>Gwai tou lup</i>	1	
<i>Teen chut</i>	1	
<i>Buk kay</i>	1	
<i>Gay zhi</i>	1	
<i>Pay pau tong</i>	1	
<i>Po chai yuen*</i>	1	
Scorpion	1	
Sea dragon	1	
Sea horse	1	
Deer Horn	1	
Misc. syrup	1	
Misc. herbal soup	1	
Misc. preparation		
<u>Teas (total)</u>	14	28%
Herbal	5	10%
Leung	2	4%
24 flavor	2	4%
<u>Other Teas:</u>	5	10%
	1	
	1	
<i>Gum lo</i>	1	
<i>Hop Jai</i>		
Flu	1	
5 flower		
Green	1	
Misc. herbal		

* * Please see Addendum: Definitions for explanations of several commonly-used TCM remedies.

*

*Notes: Some patients reported usage of multiple types of TCM while others did not specify which TCM used. One patient did not complete this section of the questionnaire

Amongst the 50 TCM-using participants: 28 (56%) used prescriptions provided by TCM practitioners, 26 (52%) used over-the-counter TCM preparations, and 14 (28%) used herbal teas. There were a total of 18 OTC TCM preparations reported, but the only two used by more than one patient were Lingzhi, used by 13 (26%) of patients, and cordyceps, used by 4 (8%) of patients. Furthermore, patients reported use of 9 types of TCM teas. Miscellaneous herbal teas were used by 5 (10%) patients while *leung* tea and 24-flavor tea by 2 (4%) of the TCM-using patients. Use of the 6 other types of TCM teas was reported by only 1 patient each.

When asked to indicate their goal(s) for TCM use, both General Health Maintenance and Treatment of Minor Illness were checked by 28 (46%) of patients. The next two most common answers, General Suppression of HIV/AIDS and Treatment of Complications Due to HIV/AIDS, were selected by 4 (8%) patients each (Table 3).

Table 3. *Goals for TCM Use*

Goal	No. Patients	
	(N=50)	Percent
General health maintenance	28	46%
Minor illness	28	46%
General suppression of HIV	4	8%
Treatment of HIV-related complications	4	8%
Treatment of HIV	2	4%
Treatment of side effects from HAART	2	4%
Major illness	1	2%

TCM users were asked to chose from a list of goals for which they use TCM. They were allowed to choose more than one answer or write-in their own.

Patients were also asked to report their reason(s) for using TCM. The two most common reasons given were Prior Evidence of Effectiveness of TCM, which was selected by 23 (46%) patients, and Recommendations from Family or Friends, which

was selected by 21 (42%) patients. Also, 9 (18%) participants reported that TCM was More Effective in Treating HIV/AIDS (Table 4).

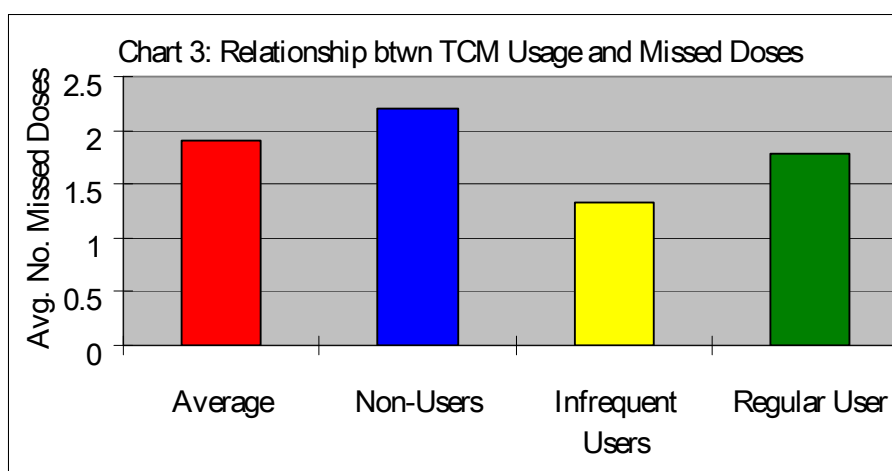
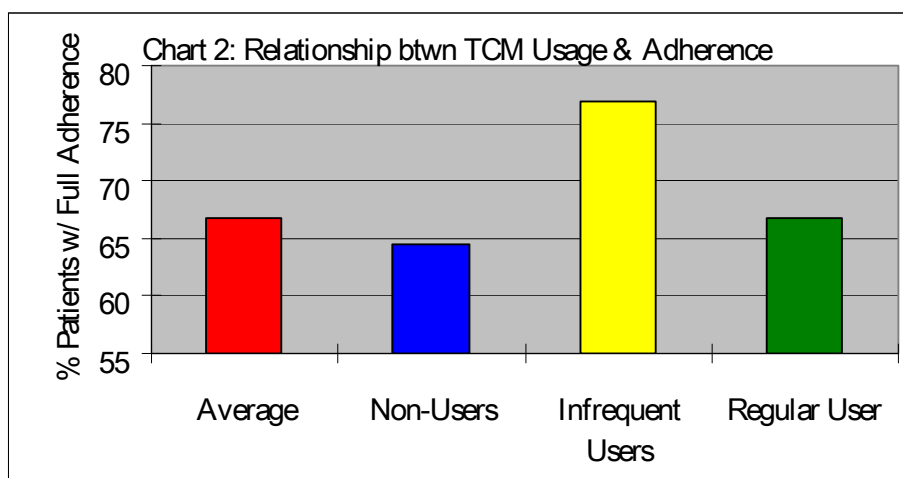
Table 4. Reasons for TCM Use

Reason	No. Patients*	
	(N=50)	Percent
Prior evidence of effectiveness	23	46%
Recommendation family/friends	21	42%
More effective	9	18%
Less side effects	5	10%
More affordable	4	8%
Use is customary	3	6%
Faster	2	4%
Recommendation ITC physicians/nurses	2	4%

TCM users were asked to choose from a list of reasons which motivated them to use TCM. They were allowed to choose more than one answer or write-in their own.

Full adherence to all doses of HAART within the past month was reported by 54 (66.7%) of participants while 27 (33.3%) patients reported having missed one dose or more within the past month. For patients that missed at least one dose within the past month, the average was 1.9 missed doses (SD= 1.04).

Adherence was then considered when patients were separated by TCM usage patterns (Charts 2 & 3). Among Non-Users, full adherence was reported by 20 (64.5%) and among the 11 (35.5%) patients that missed at least one dose within the past month, the average number of missed doses was 2.20 (SD=1.32). Meanwhile, 10 (76.9%) of Infrequent TCM-Users reported full adherence and the average number of missed doses among the 23.1% of participants that had missed at least one dose was 1.33 doses (SD=0.58). Finally, 34 (66.7%) Regular TCM Users had full adherence and 12 (33.3%) had missed at least one dose in the past month. On average, Regular TCM users that missed doses had missed 1.79 (SD=0.84) doses in the past month.



Discussion

Our hypothesis was that HIV-positive patients who used TCM would have lower HAART adherence than those who did not use TCM. Unfortunately, our results did not prove our hypothesis as there was no statistically significant difference in adherence rates between Non-Users, TCM Infrequent Users, or TCM Regular Users. Full adherence among TCM Non-Users (64.5%) and Regular Users (66.7%) were nearly identical to each other and to the study-wide average amongst all participants (66.7%). Additionally, when Non-Users and Regular Users missed doses, they missed similar numbers of doses. The similar full adherence rates between these groups suggests that TCM usage has no relationship to HAART adherence amongst this population of HIV+ males at the Hong Kong Integrated Treatment Centre.

Of note is that Infrequent TCM Users (76.9%) had the highest rates of full adherence. Moreover, Infrequent TCM Users with imperfect adherence missed fewer doses (avg=1.33) than both TCM Non-Users and Regular TCM Users. Unfortunately, our study size was too small to verify the statistical significance of these results.

Perhaps, patients who are willing to sample some forms of TCM once or twice exhibited an augmented initiative to care for themselves or a greater desire to be in control of their own healthcare decision-making, which may contribute to higher adherence rates. Research confirms that patients with a strong desire for medical information and involvement in medical decision making were more likely to use CAM, such as TCM (Hsiao et al, 2003).

We found that approximately 2/3 of patients had used some form of TCM at least once. Similarly, a 1998 study reported that 50-60% of the population of Hong Kong had sought medical advice from TCM practitioners once or more (Tang and Wong, 1998).

Overall, 13 (16%) of respondents had only sampled TCM once or twice while 36 (44%) were Regular Users. This percentage of users appears elevated from a 2001 study, which reported that 13.5% of respondents from a sample of 1,183 households in one district in Hong Kong were frequent or occasional users of TCM drugs. That study found that two factors predictive of TCM use were being female and having a chronic disease (Lau, et al, 2001).

Many studies have confirmed that use of TCM or other forms of CAM is higher among patients with chronic diseases such as HIV. Yet, CAM usage from HIV/AIDS patients has a very wide range, from 27% to 100% (Ernst, 1997). One study of gay and bisexual HIV-positive Latino men in the US found that 80% of participants had reported using some form of CAM. Among Thai patients, that number was 95% (Wiwanitkit, 2003).

Unfortunately, the aforementioned and many similar studies have one of two shortcomings making comparisons difficult. Studies either fail to give a strict definition of TCM or fail to distinguish between patient usage patterns of TCM. Most studies done on Western patient populations consider TCM just one of a large list of CAM remedies, which makes direct comparison to studies done on Eastern populations. Also, as evidenced by this study, usage patterns of TCM vary greatly and to simply ask whether or not a patient has ever used TCM oversimplifies a complex medical behavior beyond usefulness for research purposes. Until a substantial literature is created that fits these standards, our understanding of TCM will remain incomplete.

This study appears to be the first attempt to explore and inventory the forms of

TCM used by male HIV/AIDS patients in Hong Kong. As similarly conveyed in our patient interviews, the only forms of TCM used were either ingestible over-the-counter TCM preparations or herbs/herbal preparations prescribed by TCM practitioners; which were both used by more than half of participants – although some used both. Bifurcating the otherwise expansive assortment of ingestible TCM modalities into these two categories will provide a useful method for classification in future studies.

The 30 distinct types of TCM reported being used by our 51 TCM-using patients indicates the breadth of TCM products utilized. Had our study included more patients, we expect to have found an even greater number of forms of TCM. Still, we were not surprised to find nearly one-quarter of our TCM-using patients using lingzhi and a type of lingzhi called wuzhi. As TCM is very much a market-driven economy in Hong Kong, those products with the most advertising and commercial exposure are often the most sold.

Unfortunately, OTC TCM remedies are not well-regulated or overseen by the Hong Kong Department of Health; although this is changing. Prescriptions given out by TCM practitioners pose an ever greater challenge in regulation and oversight. As gathered from our interviews, patients could only report that they were given an unrecognizable assortment of herbs by their TCM practitioners with instructions for consumption. Respondents confirmed that they did not know or recall what herbs they were given. This obscure practice poses a difficult obstacle for both health department oversight and medical research into formulations and effects.

Unfortunately, given the tremendous lack of research in this field, little is known about the biological activity or possible interactions of these TCM drugs with Western medications. While this area of investigation is still burgeoning, it is hoped that results from studies such as our will point researchers into the right direction of which TCM modalities require the most immediate attention, such as lingzhi and cordyceps.

Interestingly, the majority of TCM-using patients involved in this study did not change their usage of TCM after their HIV diagnosis. No change in TCM usage was reported by about 3/4 of both Infrequent and Regular Users. Again, previous literature fails to delve into how HIV/AIDS patients have changed their TCM usage since diagnosis, if at all. Nevertheless, our findings suggest that most TCM-using patients do not consider HIV/AIDS to fall within the realm of health concerns that TCM is utilized for. Perhaps, as HIV/AIDS is a new disease when compared to the thousands of years of history of TCM, many individuals do not have the cultural experience of considering TCM to be relevant to the treatment of HIV/AIDS.

Responses regarding the reasons and goals for TCM use also attest to the cultural connection to TCM use. The two most common reasons affirmed for TCM use were

not directly related to treatment of or complications arising from HIV/AIDS. Nearly half of patients cited prior proven effectiveness of TCM and the recommendations of family and friends as reasons for using TCM. Previous use of TCM—perhaps during childhood, when medical care is largely controlled by parents and other family members— seems to continue beyond HIV diagnosis while patients who were not raised in environments that promoted on TCM were unlikely to begin TCM usage as adults or after HIV diagnosis. Hence, culture seems to be an important determinant of TCM usage by these patients, which accounts for why TCM usage rates reported across the globe vary so greatly.

Furthermore, nearly half of all TCM-using patients reported that their goals for TCM usage were general health maintenance and to treat minor illnesses. Few patients reported TCM usage for suppression of HIV infection, treatment for HIV or HIV-related complications, HAART-related side effects, or other major illnesses.

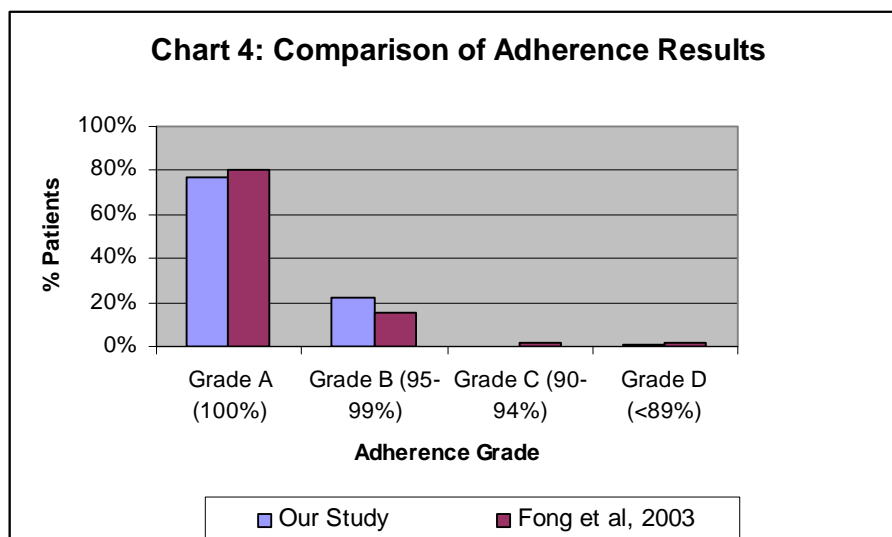
Our study's findings suggest that TCM usage by our patients is unrelated to treatment for HIV/AIDS. We assume that patients that would use TCM to treat HIV would not be regular ITC clinic attendees and would therefore not be included in our study. TCM-using patients are those that already had the habit of using TCM before diagnosis. As the high adherence levels among participants indicate, most patients rely almost exclusively on HAART to treat their HIV/AIDS-related health needs. Meanwhile, patients that did not have the custom of using TCM before diagnosis do not begin to use TCM afterwards. We hope that future studies can help elucidate this division. Nevertheless, our hypothesis that patients who used TCM would have lower HAART adherence was not proven true.

The results of our survey also corroborate the results of the Fong et al. study which found Grade A adherence among nearly 81% of 195 male and female HIV-positive patients at ITC (Fong, et al., 2003). Table 5 compares the adherence grades from both studies. In the earlier study, 79.6% of male participants had full adherence and 20.4% had partial (Fong et al, 2003). In our study, those numbers were 66.7% and 33.3%, respectively. These similarities corroborate the accuracy and reliability of both studies as well as the exceptionally high adherence rates found at ITC as compared to studies done in other countries (Table 5 & Chart 4).

Table 5. Comparisons of Adherence Results

Adherence Grade (% Adherence)	Our Study (♂ only)	Fong et al, 2003 (♀+♂)
Grade A (100%)	66.50%	80.70%

Grade B (95-99%)	22.20%	15.50%
Grade C (90-94%)	0	1.90%
Grade D (<89%)	1.20%	1.90%



Our results confirm the importance of appreciating variations in individual patterns of TCM use and HAART adherence in order to gain a better understanding of and improve the healthcare community's response to patient needs.

The aim of investigations such as ours is to understand what the healthcare community can do to ensure that patients who have access to such life-prolonging medications will have the understanding, motivation, and support necessary to achieve full adherence. Our data suggests that TCM usage does not have a significant impact on HAART adherence in these HIV-positive men. Thus, we must continue to search for more relevant social, cultural, or economic factors that facilitate or hinder full adherence.

Nonetheless, the study underscores that importance of understanding local cultural beliefs that affect all medical practices. The effect of the use of Traditional Chinese medicine by these men in Hong Kong will not be the same as other traditional medical cultures in other settings. These cultural forces are largely responsible for all facets of health and disease and deserve the continued attention of medical researchers as it is impossible to separate disease from the population that it affects.

Study Limitations

Our results are limited by our study size, which is smaller than those of similar studies. However, this shortcoming has been mitigated by limiting our results to one gender and by the personal interviews conducted at the beginning of our study, which helped us to focus the scope and detail of our questionnaire.

Also, the patient pool may not necessarily reflect the TCM-usage patterns of the larger Hong Kong population. All patients who attend ITC have already chosen to receive Western medical care and may not encompass the views and opinions of patients who have chosen to only utilize TCM. Therefore, we expect that our results would underestimate TCM usage among all HIV/AIDS patients as those patients who do not receive care from Western medical clinics in Hong Kong are more likely to use TCM.

Another drawback is the inherent difficulty in defining and limiting what is considered TCM, which confounds attempts to compare our results with those of similar studies. Many principles of TCM are so engrained in Chinese culture that the distinctions between medicine, food/diet, and daily lifestyle are often difficult to draw. Herbal teas and soups are drunk on such a regular basis that some patients may not consider them medicinal. Similarly, some studies may decide to include such herbal teas and soups in their definition of TCM while others may not. During our study, we intentionally provided patients a very loose definition of TCM in hopes of gaining a broad perspective of patient behaviors and opinions. We hope that our study underscores the importance of providing a clear definition of TCM to both study participants and other researchers.

A further limitation on the study's ability to shed light on TCM use's influence on HAART adherence is that ITC patients have an exceptionally high level of adherence partly due to a meticulous program during which patients are informed of the importance of full adherence before beginning the HAART regimen. Patients are also warned low adherence may be worse than not taking HAART at all so individuals likely to have low adherence often choose not to begin treatment and would likely not be included in our study. Nevertheless, by elimination patients whose imperfect adherence might be accounted for by other reasons, our study is able to focus on those patients whose adherence might be greater influenced by TCM usage.

There are several shortcomings to adherence studies in general. When relying on patient self-report of missed doses, we expect that memory bias and other psychological factors account for an under-reporting of the actual number of missed doses. However, we hoped to minimize this drawback by only asking patients about missed doses in the past month and by reminding patients at the beginning of the

study that their responses would have no effect on their clinical care by ITC physicians and nurses.

A second limitation is the intrinsic weakness of measuring adherence solely by the number of missed doses. Like TCM usage, adherence is complex medical issue that is oversimplified when merely quantified as a percentage of missed doses. For instance, taking a dose off-schedule or without observing diet restrictions may prove even more detrimental than missing a dose entirely. Besides simply calculating adherence, we hoped to gain a better understanding of adherence patterns by asking patients about which doses they missed and to report factors that encouraged them to adhere or to miss doses.

One element which distinguishes ITC from the settings of other similar studies is the impact of finances of patient decision-making. For HIV/AIDS patients in Hong Kong, Western-style clinical care and prescription medications offered by the ITC are heavily subsidized by the government. A month's supply of HAART costs patients HKD 30 (\$4.30 US) and patients that cannot afford such prices are offered drugs at a reduced price or for free. Meanwhile, any visits to TCM practitioners and TCM remedies bought must be purchased out-of-pocket by patients so that—unlike in most Western settings—TCM care is much more costly than Western medicines. In fact, studies have suggested that higher income groups are more likely to purchase traditional food supplements (Ho and Donnan, 1985). For instance, one month's supply of cordyceps at a local drug store chain can cost more than HK \$800 (US \$100). Thus, we expect that cost would have been much more of a consideration for patients seeking TCM care rather than Western medical care. Yet, this financial situation unique to Hong Kong allows us to diminish the importance of cost on adherence, as we expect HAART-related expense to have little or no impact on adherence.

We hope that this study will point further research in the direction of exploring potential adverse interactions between TCM and HAART. As there is little research regarding most TCM therapies, little is known about their biological activity. By beginning to understand the extent of TCM therapies used by patients, we hope to set the stage for further investigations into the potential effects and actions of these TCM alone and alongside Western medications. We hope further research will resume our efforts to understand how to improve the treatment of patients in setting where these two medical cultures continue to simultaneously coexist and interact.

Addendum: Definitions

Cordyceps, *cordyceps sinensis*. *Sphaeria sinensis*

aka: Chinese caterpillar fungus, *dong chona xia cao*

Cordyceps includes fungus that grows on the larvae of the caterpillar, *hepialus armoricanus* Oberthuer. Both are contained in the product and both are consumed.

Cordyceps is used for a wide range of conditions including fatigue, sexual dysfunction, coughs, and as an adaptogen or immune stimulant.

Lingzhi, *Ganoderma lucidum*

aka: Reishi mushroom, Mushroom of Immortality

Derived from the cap and stem of the mushroom. The active constituents are thought to include both beta-glucan polysaccharides and triterpenes. Reishi mushroom is used as an immune stimulant by patients with HIV and cancer.

Tai Chi

aka: tai chi chuan,

Tai chi is an exercise program that uses a sequence of precise body movements, meditation, and synchronized breathing to improve health and well-being. Tai chi movements are designed to express the yin and yang components that are fundamental to Chinese medicine in a balanced and harmonious form.

Acupuncture

Acupuncture treatment involves the stimulation of one or more predetermined points on the body with needles, heat (moxibustion), pressure (acupressure), or electricity for therapeutic effect.

Qi Gong

Practitioners of Traditional Chinese Medicine believe that disease results when the flow of Qi (internal energy) is blocked and when there is disharmony between yin and yang forces. Tai chi exercises are thought to result in balancing these forces and promoting the flow of Qi to improve health. “Gong” means “work” in Cantonese.

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